H 5.1
Appeal Brief

In the United States Patent and Trademark Office

In re Cederholm-Williams	:	BOARD OF PATENT APPEALS AND INTERFERENCES
Serial No.: 09/334,325	:	
Filing Date: June 16, 1999	:	
For: Fibrin Sealant As A Transfection/Transformation Vehicle For Gene Therapy	:	PATENT APPEAL
Docket No.: CV0276A	:	
Art Unit: 1632	:	
Examiner: Chen, Shin Lin	:	

APPELLANT'S APPEAL BRIEF

12/05/2002 MGEBREM1 00000119 09334325

01 FC:1402 320.00 OP
~~02 FC:1251 110.00 OP~~

DECHERT PRICE & RHOADS
Princeton Pike Corporate Center
P.O. Box 5218
Princeton, NJ 08543-5218
(609) 620-3200

Attorneys for Appellant

ALLEN BLOOM
ARTHUR E. JACKSON
THOMAS S. DEIBERT
On the Brief

141966.1.07

TABLE OF CONTENTS

TABLE OF AUTHORITIES

FEDERAL CASES

STATUTES

OTHER

1. **Real Party in Interest**

The inventors have assigned their interest to Bristol-Myers Squibb Company. Accordingly, Bristol-Myers Squibb Company is the real party in interest.

2. **Related Appeals and Interferences**

On information and belief, there are no other appeals or interferences that will directly affect or have a bearing on the Board's decision in this Appeal.

3. **Status of the Claims**

Claims 1, 2 and 13-16 are in the application. All other claims have been cancelled. All of the pending claims are subject to one or more rejections under 35 U.S.C. §§ 112, first paragraph, and 103(a). Claims 1, 2 and 13-16 are appealed.

4. **Status of Amendments Filed After Final**

No amendments to the specification or claims were submitted in the After Final response to the June 5, 2002 Office Action (Paper No. 18). Accordingly, the claims are in the form submitted in a response filed April 18, 2002. The pending claims are attached as Appendix A.

5. **Summary of Invention**

The invention relates to transforming cells with nucleic acid entrapped in fibrin used to maintain its contact with the cells targeted for transformation. Genetic transformation is a process whereby a cell acquires non-native genetic information and expresses it. In the present application, a transformed cell is defined as a cell where "a nucleic acid is recombinantly introduced into it or its ancestor so as to temporarily or stably (1) cause the cell to express a polypeptide or RNA in an amount not otherwise expressed by the cell or (2) interfere with the translation or transcription of a nucleic acid normally found in the cell." Specification at 21:6-9.

Thus, lead claim 1 is to:

A method of transforming a cell comprising the steps of:

applying a transformation effective amount of a nucleic acid to the cell;

adhering a pliable, adhesive fibrin gel to the cell so as to entrap a transformation effective amount of the nucleic acid in the fibrin gel adhered to the cell; and transforming the cell with the nucleic acid.

In a favored embodiment, the transformation uses a composition of fibrin stabilized in monomer form, which allows the polymer to be rapidly formed, helping to assure it acts to keep the nucleic acid in contact with the target cells. This embodiment is reflected in claims 15 and 16.

6. **Issues**

The issues are:

(a) Issue 1: Does the specification, and extensive knowledge in the art at the time of filing, enable one of skill in the art to transform a cell *in vivo* by applying a nucleic acid and a pliable, adhesive fibrin gel to said cell?

In one aspect, this issue is whether the applicant has enabled the invention. Notwithstanding, the basis of the rejection is an assertion that the application fails to demonstrate that the invention works. Thus, the 35 U.S.C. § 112 rejection is simply a rejection under 35 U.S.C. § 101 in the guise of a rejection under 35 U.S.C. § 112. Hence, the first issue addressed herein is whether the Office, when making a rejection such as this, can escape the constraints imposed by the case law of the Court of Appeals for the Federal Circuit on 35 U.S.C. § 101, or the Office's own arduously developed standards therefore, simply by framing the rejection as one under 35 U.S.C. § 112. Because it is respectfully submitted that the answer to the issue framed in the previous question is no, the rejection will be analyzed under the Office's Utility Examination Guidelines. Federal Register, Volume 66, Number 4, January 5, 2001. Last, the rejection will be analyzed under the precedent of the Court of Appeals for the Federal Circuit.

(b) Issue 2: Are claims 1, 2 and 13-16 obvious in view of the teachings of U.S. Patent No. 5,833,651 (Donovan)?

7. **Grouping of claims**

The rejection under 35 U.S.C. § 112, first paragraph, may be decided on the basis of claim 1. As to the analysis of the claims regarding the rejection under 35 U.S.C. § 103(a), claims 2 and 13-14 stand or fall with claim 1 and claims 15 and 16 must be separately analyzed for patentability. The additional limitations found in each of dependent claims 15 and 16 are not taught or suggested by the cited documents taken alone or in combination.

8. **Argument**

(a) **Rejection Under 35 U.S.C. § 112, First Paragraph - Enablement**

Claims 1, 2, and 13-16 stand rejected. The Office asserts that the rejection is for lack of enablement under 35 U.S.C. § 112, first paragraph, and is distinct from a rejection under 35 U.S.C. § 101 asserting inoperability. Specifically, the Office asserts that

> the specification, while being enabling for a method of transforming a cell *in vitro* by applying a nucleic acid and a pliable, adhesive fibrin gel to said cell, does not reasonably provide enablement for a method of transforming a cell *in vivo* by applying a nucleic acid and a pliable, adhesive fibrin gel to said cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 12-19-01 (Paper No. 15). Applicant's arguments filed 4-18-02 have been fully considered but they are not persuasive.
>
> Applicant argues that it is well known in the art that *in vivo* transfection can give rise to immune response and there are more than sufficient vectors in the art which are not disabled in their effect by an immune response. Applicant further argues that vector-based vaccines were known and desirable and are enabled

(amendment, p. 2, 3). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 12-19-01 (Paper No. 15) and that the specification fails to provide adequate guidance and evidence to enable the use of nucleic acid and pliable, adhesive fibrin gel as a vaccine in the claimed method to stimulate immune response *in vivo*. No evidence of record indicates that the nucleic acid itself can stimulate sufficient immune response in a subject *in vivo* so as to provide therapeutic effect for a particular disease or disorder. In case that the protein product encoded by the nucleic acid is desirable to stimulate immune response *in vivo*, there is no evidence of record that indicates sufficient protein product is expressed in vivo to stimulate sufficient immune response *in vivo* for treating a particular disease or disorder. Thus, the specification fails to provide enabling disclosure for the use of nucleic acid and pliable, adhesive fibrin gel as a vaccine in the claimed method of stimulate immune response *in vivo*.

In fact, the intended use of the nucleic acid and pliable, adhesive fibrin gel is for gene delivery in *in vivo* gene therapy in light of the specification (see specification, p. 2-4). As discussed in the preceding Official action mailed 12-19-01 (Paper No. 15), host immune response poses problems to the use of various vector and virus in gene transfer *in vivo*. Further no teachings are present within the specification in regard to how to transform cells with any nucleic acid in any vector or any virus containing said nucleic acid by using fibrinogen composition or fibrin gel, **how the nucleic acid entrapped in fibrin gel can be taken up by cells**, and whether the nucleic acid taken up by cells can be expressed in said cells *in vivo*. Thus, the specification fails to provide enabling disclosure for the use of nucleic acid and pliable, adhesive fibrin gel for gene delivery *in vivo*. One skilled in the art at the time the of the invention would require undue experimentation to practice over the full scope of the invention claimed.

(Paper No. 18, p. 2-4)(emphasis added).

(i) The Rejection Fails to Conform to Office Guidelines

That the nature of the rejection focuses on the text presented above in added **bold** is clear from the text presented above in added underline. That is, the text in added underline acknowledges that the description of how to make the transforming composition is indeed in the application, and that transforming

nucleic acids are well-known. Implicit in this acknowledgement is that those of ordinary skill who have undertaken many transformations know how to measure for such transformation. What is left is what is emphasized in **bold**--the Office's assertion regarding the specification's teachings relative to how the nucleic acid entrapped in fibrin gel can be taken up by cells.

(ii) Can the Office Avoid the § 101 Structure of Analysis by Asserting Only the Sister Rejection under § 112?

The first question is whether, when the basis of the rejection is an assertion of inoperativeness, can the Office avoid the burden-shifting structures imposed by the courts and published Office policy merely by framing the rejection as a rejection under 35 U.S.C. § 112. The answer to this question is provided by the Court of Appeals for the Federal Circuit in In re Cortwright, 165 F.3d 1353, 49 USPQ2d 1464 (Fed. Cir. 1999). In Cortwright, the Board of Patent Appeals and Interferences reversed a rejection under 35 U.S.C. § 101, but imposed an analogous rejection under 35 U.S.C. § 112, first paragraph. The Federal Circuit implicitly accepted that the framing of the rejection under 35 U.S.C. § 112, first paragraph, was acceptable, but imposed exactly the same burden shifting procedure for analyzing the propriety of that rejection as would be imposed for a similar rejection under 35 U.S.C. § 101, citing the same precedent-setting cases relevant to § 101. Cortwright at 1356-57, 49 USPQ2d at 1466. Similarly, in In re Brana, the Federal Circuit reviewed a rejection for want of operativeness, made by the examining corps and the Board on the basis of 35 U.S.C. § 112, under the parameters developed for rejections under 35 U.S.C. § 101. 51 F.3d 1560, 1565, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). Moreover, one of the earliest decisions relied upon by the courts as presenting the mode of analysis under § 101 was in fact decided with respect to 35 U.S.C. § 112. See In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). Thus, it is clear that even though a rejection for want of operativeness implicates 35 U.S.C. §

112, the proper mode of analysis for such a rejection remains that set forth in the case law relating to 35 U.S.C. § 101.

(iii) The Rejection Fails to Conform to Office Guidelines

Because the subject rejection was for want of utility, it was incumbent on the Office to present sufficient reason to doubt Applicant's assertion of utility. One way to seek to conform to the legal requirements for such a rejection would be to follow the Office's own internal guidelines--the Utility Examination Guidelines. While the burden on the Office to justify an assertion of want of a credible utility would appear more relaxed in the guidelines than in the precedent of the Court of Appeals for the Federal Circuit, even this low hurdle was not met in the subject rejection.

The Office's Utility Examination Guidelines require:

> Any rejection based on lack of utility should include a detailed explanation why the claimed invention has no specific and substantial credible utility. Whenever possible, the examiner should provide documentary evidence (e.g., scientific or technical journals, excerpts from treatises or books, or U.S. or foreign patents) to support the factual basis for the prima facie showing of no specific and substantial credible utility. *If documentary evidence is not available, the examiner should specifically explain the scientific basis for his or her factual conclusions.*

(Guidelines at §B.3.). Applicant submits that the rejection does not specifically explain a scientific basis to doubt the Applicant's utility. To the contrary, in the making the subject rejection, the Office turns the burden, which the Office's own rules specifically places on itself, onto the Applicant, requiring proofs. For instance, the Office asks the Applicant to explain "how the nucleic acid entrapped in fibrin gel can be taken up by cells." Applicant respectfully notes that even the most skilled in the art can offer no more than informed speculation on the mechanism of transformation. Such is not a requirement of the patent law. That is, the patent law does not require an applicant to understand the theory of operation for his or her invention.

Implicit in the Office's assertion is a belief that the nature of a fibrin gel would somehow disable transformation. That *belief* is not shared by the Applicant. Moreover, the Office's

guidelines require that the Office explain any reasoning behind this belief, so that Applicant has a real opportunity to respond.

Moreover, according to the Guidelines, the Office's showing must contain the following:

> (1) An explanation that clearly sets forth the reasoning used in concluding that the asserted specific and substantial utility is not credible;
>
> (2) Support for factual findings relied upon in reaching this conclusion; and,
>
> (3) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art.

(Guidelines at §B.3.(b).). In other words, the Office must tell the Applicant, in factually supported detail, why it believes that entrapping nucleic acid in fibrin will interfere with the transformation process. The Office's showing must, moreover, establish not that the Examiner believes that fibrin polymer interferes, but that "it is more likely than not that a person skilled in the art would not consider credible any specific and substantial utility asserted by the applicant for the claimed invention." Guidelines at §B.3.(b).

Accordingly, the subject rejection does not meet even the minimal requirements of the Utility Guidelines. Because, as will be seen, the amount of proof required to shift the burden to the Applicant under the guidelines is low, the Office's failure to meet this minimal requirement mandates a reversal of the subject rejection.

(iv) Legal Standard for Reversing the Burden Onto the Applicant

The Court of Appeals for the Federal Circuit has reiterated that:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of Section 112 unless

atcheting

a

date

at the

. Id. at

ıd the

e of

ead-bolt

concern

latter."

vice with

vidence

ce cited,

ence does

5 U.S.C.

art in no

g fibrin

olubilized

claims

CONCLUSION

For the foregoing reasons, Appellant respectfully requests that the rejections under 35 U.S.C. § 112 and 35 U.S.C. § 103(a) with respect to all of the pending claims, namely claims 1, 2 and 13-16, be reversed and the pending claims in the application allowed.

Thomas S. Deibert, Reg. No. 40,984
Arthur E. Jackson, Reg. No. 34,354
Allen Bloom, Reg. No. 29,135
DECHERT PRICE & RHOADS
Princeton Pike Corporate Center
P.O. Box 5218
Princeton, NJ 08543-5218
(609) 620-3200

Attorneys for Appellant

Dated: November 27, 2002

Appendices:

A: Claims on Appeal.

APPENDIX A - COPY OF CLAIMS ON APPEAL

not sequential

1. A method of transforming a cell comprising the steps of: applying a transformation effective amount of a nucleic acid to the cell; adhering a pliable, adhesive fibrin gel to the cell so as to entrap a transformation effective amount of the nucleic acid in the fibrin gel adhered to the cell; and transforming the cell with the nucleic acid.

2. The method of claim 1, wherein the nucleic acid is applied in admixture with a fibrin or fibrinogen composition that forms the pliable, adhesive fibrin gel.

112 2nd

13. The method of claim 1, wherein the nucleic acid is a plasmid.

14. The method of claim 1, wherein the nucleic acid is incorporated in a virus.

15. The method of claim 1, wherein the pliable, adhesive fibrin gel is formed by mixing a fibrin monomer composition with a polymerizing agent preparation effective to convert the fibrin monomer preparation into a fibrin gel, and adhered by contacting the cell with the mixture while the mixture is pliable and adhesive.

16. The method of claim 15, wherein the fibrin monomer composition comprises acid-solubilized fibrin, and the polymerizing agent comprises an amount of base effective to sufficiently neutralize the mixture to allow the fibrin to polymerize.

Claim 1. 11 comprising (Seq. step is unclear. functioning fibrin gel is to hold NA.

112 2nd 1, 2

112 1st enable stent or balloon but not supported by spec. emphasis on how to apply in vivo

102/103